REMARKS

Claim Amendments

Claims 1, 3, 4, 5, 7-11, 13, 15, 16, 20, 22-25, and 26-30 are pending in this application. With the present submission, claim 6 has been cancelled without prejudice or disclaimer. Claims 1and 16 have been amended. New claims 26-30 have been added.

Claim 1 has been amended to recite that the assay system is a cell proliferation assay system employing mammalian cells and to recite steps for measuring cell proliferation in the absence and presence of a test agent that modulates the expression of CSNK1G. Support for the amendment can be found throughout the specification, for example, at pages 2-3, 19, 23, 24 (particularly lines 27-31) and in original claim 6.

Claim 16 has been amended to recite that the second assay system comprises mammalian cells and detects a phenotypic change in the p21 pathway, that the second assay system is contacted with the test agent, and that detection of a phenotypic change in the p21 pathway between the second assay system contacted with test agent and the untreated second assay system confirms the test agent as a candidate p21 modulating agent. Support for the amendment can be found throughout the specification, for example, at pages 29 and 30 (particularly lines 6-11) and in original claim 16.

New claims 26-30 are drawn to subject matter found in original claims 7, 8, 9, 10, and 11, which represent Inventions II-VII. According to the Office, Claim 1 links Inventions I-VII. Upon allowance of claim 1, the restriction requirement as to the linked inventions shall be withdrawn and any claim depending from or otherwise including all the limitations of the allowable linking claim will be entitled to examination in the instant application.

New claim 26 recites "[t]he method of Claim 1, wherein the candidate test agent is an anti-CSNK1G antibody." Support for the amendment can be found throughout the specification, for example, at pages 15-17, and in original claim 7.

New claim 27 recites "t]he method of Claim 1, wherein the candidate test agent is a nucleic acid modulator that modulates CSNK1G expression." Support for the amendment can be found throughout the specification, for example, at pages 17-19, and in original claim 8.

New claim 28 recites "[t]he method of claim 27, wherein the nucleic acid modulator is an antisense oligomer directed against CSNK1G nucleic acid." Support for the amendment can be found throughout the specification, for example, at page 18, and in original claim 9.

New claim 29 recites "[t]he method of Claim 28, wherein the nucleic acid modulator is a PMO." Support for the amendment can be found throughout the specification, for example, at page 18, and in original claim 10.

New claim 30 recites "[t]he method of Claim 1 additionally comprising: (d) administering the candidate p21 pathway modulating agent identified in (c) to a model system comprising cultured cells defective in p21 function and detecting a phenotypic change in the model system that indicates p21 function is restored." Support for the amendment can be found throughout the specification and in original claim 11.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice or disclaimer, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. Additionally, these amendments and cancellation are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. No new matter has been added by way of these amendments. Accordingly, Applicants respectfully request the entry of the amendments presented.

Claim Objections

Claims 1-3 and 16 were objected to for allegedly reciting non-elected subject matter. Without acceding to the merits of the objection, Applicants have amended claim 1 to address the objection. Applicants respectfully request withdrawal of the claim objections.

The 35 USC § 101 Rejection

Claims 1, 3, 6 and 16 were rejected under 35 USC § 101 because the claimed invention allegedly lacks patentable utility. Specifically, the Office alleged that the claims lack a specific and substantial utility. Applicants submit that claim 6 has been canceled, rendering the rejection

moot as to that claim. With respect to the pending claims, Applicants respectfully traverse the rejections.

The Office alleged that the presently claimed methods lack utility because the method "is designed to merely identify a 'candidate' p21 pathway modulator. Thus, the method fails to have a specific and substantial benefit to the public without further research to determine if the 'candidate' modulator is, in fact, a modulator of the p21 pathway. Practicing the recited steps has no immediate benefit to the public."

An invention has specific utility if the identified use is well-defined and has a particular benefit to the public and is specific to the subject matter claimed. As explained in the specification, p21 is involved in the regulation of cell growth. Specifically, p21 is a cell cycle control protein that inhibits cyclin-kinase activity and mediates p53 suppression of tumor cell growth. (specification, page 1). Applicants have discovered that casein kinase I (CSNK1G), a serine/threonine kinase, modifies the p21 pathway. (specification, at pages 2-3). As explained in the specification, CSNK1G proteins and nucleic acids can be used to identify p21 modulating agents. The identification of such agents can be used in the study and treatment of disorders associated with defective or impaired p21 function, such as cancer . (specification, at pages 2-4). Thus, the invention provides screening assays that have specific utility for identifying p21 pathway modulating agents, which agents are candidates for the further development of diagnostic and therapeutic modalities for the diagnosis and treatment of disorders associated with defective p21. The specification describes additional uses at pages 32-34.

A claimed invention has substantial utility if it defines a "real world" or "practical" use. According to the MPEP, "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility". MPEP §2107.01 I. The claimed methods have a practical use for identifying p21 pathway modulating agents, which agents are therapeutic candidates for the diagnosis and treatment of disorders associated with defective p21.

The Office asserted that the present claims fail to have a specific and substantial benefit to the public without further research to determine if the 'candidate' modulator is, in fact, a modulator of the a p21 pathway. The Office concluded that the recited steps have no immediate

benefit to the public. However, contrary to the Office's assertion, the claimed invention does indeed have an immediate benefit to the public. Applicants have discovered that CSNK1G modulates the p21 pathway. Thus, among other things, the claimed screening assays employing CSNK1G polypeptides or nucleic acids have the immediate benefit of identifying those compounds that modulate p21. The fact that the identified compounds may require additional testing to confirm p21 pathway modulation does not detract from the invention's immediate benefit of identifying specific compounds (out of potentially hundreds of compounds) that modulate p21. Furthermore, the fact that further research may be indicated does not preclude a finding of substantial utility. In this regard, the Federal Circuit has specifically determined that the term "benefit to the public" is not interpreted "to mean that products or services based on the claimed invention must be 'currently available' to the public in order to satisfy the utility requirement." MPEP §2107.01, citing *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966).

Finally, Applicants point out that the Patent Office itself has recognized the utility of identifying "candidate" test agents. Several patents have issued with claims similar to the instant application. See, for example, US Patent Nos. 7,507,547; 7,501,395; 7,504,227; 7,498,134; and 7,498,127.

For the reasons discussed above, the pending claims have specific and substantial utility. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §101 rejections.

The 35 USC § 112, Second Paragraph, Rejections

Claims 1, 3, 6, and 16 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite. Applicants submit that claim 6 has been canceled, rendering the rejection moot as to that claim. With respect to the pending claims, Applicants respectfully traverse the rejections.

Specifically, the Office stated that the phrase "agent-biased activity" renders the claims indefinite. Without acceding to the merits of the rejection, and solely in an effort to advance prosecution, claims 1 and 16 have been amended to remove the phrase "agent-biased activity".

In addition, the Office stated that the phrase "the system" lacks antecedent basis. Claim 1 has been amended, thereby rendering the rejection moot.

The Office also stated that the phrase "CSNK1G polypeptide" renders the claims indefinite. Without acceding to the merits of the rejection, and solely in an effort to advance prosecution, claims 1 and 16 have been amended to recite that the CSNK1G polypeptide is a full-length, wildtype CSNK1G polypeptide. Support for the amendment can be found throughout the specification, for example, at page 4. Applicants believe that the phrase "full-length, wildtype CSNK1G polypeptide" clearly delineates the metes and bounds of the recited invention.

For the reasons discussed above, the pending claims are clear and definite. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejections.

The 35 USC § 112, First Paragraph, Rejections

Enablement

Claims 1, 3, 6, and 16 were rejected under 35 USC § 112, first paragraph, as allegedly not being enabled. Applicants submit that claim 6 has been canceled, rendering the rejection moot as to that claim. With respect to the pending claims, Applicants respectfully traverse the rejections.

Applicants submit that the instant claims satisfy the enablement requirement for all of the reasons set forth in the previous response filed on January 14, 2008, which response is incorporated herewith.

Despite Applicants arguments, the Office maintained that the claims are not enabled because the specification allegedly fails to teach the full scope of the recited invention, which encompasses any method for identifying a candidate p21 pathway modulator by assessing the proliferation of any cultured cell expressing any CSNK1G.

However, the claims have been amended to recite a method for identifying a candidate p21 pathway modulator employing a mammalian cell that expresses a full-length, wildtype CSNK1G polypeptide or nucleic acid in a cell proliferation assay system and a test agent that modulates the expression of CSNK1G. In this regard, the specification clearly describes and provides examples of cultured mammalian cells that can be used, including for example, HCT116 colon cancer cells, LX1 small lung cancer cells, 231T breast cancer cells, and A549

lung cancer cells (pages 30, 37-39). In addition, as the Office clearly recognized, it was known in the art that CSNK1G is ubiquitously expressed in mammalian cells (see Kusuda et al. 2000).

The specification at pages 4-5 also clearly describes and provides examples of full-length wildtype CSNK1G polypeptides and nucleic acids, including, for example, those CSNK1G molecules having SEQ ID NOs: 1-16. The specification further teaches methods for obtaining additional CSNK1G sequences (pages 7-9). Moreover, one skilled in the art would know how to obtain the sequences of any additional full length wildtype CSNK1G polypeptides or nucleic acids using a public database, such as GenBank.

The specification further provides numerous examples of test agents that modulate the expression of CSNK1G, including CSNK1G-interacting proteins (such as CSNK1G antibodies), and nucleic acid modulators (such as CSNK1G antisense and siRNA) at pages 12- 19.

In addition, the specification at pages 23-25 clearly describes and provides examples of appropriate cell proliferation assays that can be used in the claimed methods, including for example, BRDU incorporation assays, phospho-histone H3 staining assays, [^{3}H]-thymidine incorporation assays, MTS assays, soft agar assays, assays that measure ATP levels, as well as other assays.

Thus, the specification thoroughly teaches one skilled in the art how to make and use the claimed methods.

In addition, the Office argued that the claims are not enabled because neither the specification nor the prior art allegedly provide evidence that a response of proliferation is diagnostic for modulation of the p21 pathway in any particular cell types. The Office asserted that non-p21 pathways could be modulated by the test agent, which pathways could affect cell proliferation, and therefore a skilled artisan would not be able to deduce whether a test agent affecting cell proliferation of a cell expressing CSNK1G is a p21 pathway modulator. The Office concluded that it would require undue experimentation for the skilled artisan to determine whether the p21 pathway is the sole pathway that mediates proliferation in all cell types.

Contrary to the Office's contentions, Applicants submit that one skilled in the art would be able to practice the claimed invention without undue experimentation. First, the specification clearly teaches that the p21 pathway is modulated by CSNK1G, as evidenced by the Drosophila data provided and discussed on pages 1-3 and 34. Applicants' findings clearly show that the CG6963 gene modifies the p21 pathway and that the vertebrate orthologs of the CG6963 gene are the CSNK1G genes. As explained in the specification, the Drosophila model used to

generate this data provides a powerful means to analyze biochemical processes that have direct relevance to complex vertebrate organisms due to the significant evolutionary conservation. In support of the Drosophila model used by the Applicants, the specification cites numerous scientific articles that teach that, due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals. Drosophila is a well-known research tool and is extensively utilized as a model of human disease, especially for understanding novel genes (Adams & Sekelsky, Nature Reviews, 3: 189-198 (2002)). The scientific community's understanding of many human genes is due to research in Drosophila (Chintapalli et al., Nature Genetics, 39(6); 715-720 (2007)). The Chintapalli reference specifically confirms the usefulness of the Drosophila system to identify the gene function of human genes involved in disease and discusses several human homologs in a variety of tissues and pathways that were discovered using the Drosophila model.

Second, as taught in the specification and known in the art, the p21 pathway is involved in the regulation of cell growth and proliferation. See specification at page 1 and Funk et al. (2000) (cited by the Office). Moreover, Applicants have demonstrated that CSNK1G is overexpressed in various tumor cell lines (pages 37-38) and have also demonstrated that siRNA against CSNK1G (ie, decreased CSNK1G expression) decreases proliferation in LXI, 231T, and A549 cells as measured by BrdU, Cell Titer-Glo and MTS proliferation assays (pages 38-39).

Finally, the specification teaches that one can use cultured cells or animal models defective in p21 to confirm that the test agent is modulating the p21 pathway and that the p21 pathway is mediating cell proliferation. For example, the specification teaches that cultured cells having altered or defective p21 expression can be used, for example, HCT116 colon cancer cells, among others available from the ATCC. (specification at pages 12, 24-25, and 30). In addition, the specification teaches that genetically modified animals having altered p21 expression, such as p21 knock-out or p21 knock-in animals, can be used to further assess the role of CSNK1G in a p21 pathway process, such as cell proliferation. (specification at pages 9-12 and 30). The specification teaches methods for obtaining such transgenic animals and indicates that p21 knock-out mice are also known and described in the literature. Thus, this type of testing involves cells, animal models, methods and techniques well-known in the art and thus would not be considered undue experimentation for the skilled artisan.

For the reasons discussed above, the pending claims are enabled. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejections based on lack of enablement.

Written Description

Claims 1, 3, 6, and 16 were rejected under 35 USC § 112, first paragraph, as allegedly lacking written description. Applicants submit that claim 6 has been canceled, rendering the rejection moot as to that claim. With respect to the pending claims, Applicants respectfully traverse the rejections.

Applicants submit that the instant claims satisfy the written description requirement for all of the reasons set forth in the previous response filed on January 14, 2008, which response is incorporated herewith.

Despite Applicants arguments, the Office maintained that the claims do not satisfy the written description requirement because the specification allegedly fails to sufficiently describe the recited invention which encompasses any method for identifying a candidate p21 pathway modulator by assessing the proliferation of a cultured cell expressing CSNK1G. Specifically, the Office stated that specification fails to sufficiently describe the use of any cell comprising any CSNK1G polypeptide. In addition, the Office asserted that the specification fails to sufficiently describe those cells that can be used successfully in the elected invention, ie those cells having the characteristic that their proliferation is mediated solely by the p21 pathway.

However, the claims have been amended to recite a method for identifying a candidate p21 pathway modulator employing a mammalian cell that expresses a full-length, wildtype CSNK1G polypeptide or nucleic acid in a cell proliferation assay system and a test agent that modulates the expression of CSNK1G.

Contrary to the Office's allegation, the specification sufficiently describes and provides a representative number of exemplary cultured mammalian cells that can be used in the claimed methods, including for example, HCT116 colon cancer cells, LX1 small lung cancer cells, 231T breast cancer cells, and A549 lung cancer cells, as discussed above. In addition, as the Office clearly recognized, it was known in the art that CSNK1G is ubiquitously expressed in mammalian cells (see Kusuda et al. 2000).

Furthermore, as discussed above, the specification also sufficiently describes and provides a representative number of exemplary full-length, wildtype CSNK1G polypeptides and

nucleic acids, including, for example, those CSNK1G molecules having SEQ ID NOs: 1-16. Moreover, one skilled in the art would know how to obtain the sequences of any additional full length wildtype CSNK1G polypeptides or nucleic acids using a public database, such as GenBank.

With respect to the Office's implication that only those cells having the characteristic that their proliferation is mediated solely by the p21 pathway are useful in the instantly claimed methods, Applicants respectfully disagree. As taught in the specification and known in the art, p21 is involved in cell proliferation. As taught in the specification, CSNK1G modulates the p21 pathway. Therefore, it is logical to monitor the effects of a test agent (that modulates CSNK1G expression) on p21 using cell proliferation as a phenotypic marker. Furthermore, as taught in specification and known in art (see Funk et al and Donato et al), there are more appropriate ways of confirming whether the p21 pathway is being modulated than to use "cells having the characteristic that their proliferation is mediated solely by the p21 pathway". For example, as taught by the specification, standard methods for assessing whether the p21 pathway is being mediated by the test agent in a cell proliferation assay would involve using cells or animal models that have a defective p21 pathway, such as HCT116 colon cancer cells and transgenic p21 knock-out animals. Other cells can be made to have a defective p21 pathway by transfecting the cells with antisense or siRNA against p21 to eliminate the p21 pathway. Although Applicant submits that such assessment is not required, this type of testing to directly confirm p21 modulation involves cells, animal models, methods and techniques described in the specification and otherwise known in the art.

For the reasons discussed above, the pending claims satisfy the written description requirement. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph, rejections based on lack of written description.

The 35 USC § 102 Rejections

Claims 1, 2, 3, 6, and 16 were rejected under 35 USC § 102 (b) as allegedly being anticipated by Funk et al. (J. Immunol. 165: 4792-4796 (2000)) as evidenced by Kusada et al. (Cytogenetics and Cell Genetics, 90: 298-302 (2000)). Applicants submit that claims 2 and 6 have been canceled, rendering the rejection moot as to those claims. With respect to the pending claims, Applicants respectfully traverse the rejections.

Funk et al. fails to anticipate the claimed invention. A claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. M.P.E.P. §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226 (Fed. Cir. 1989); M.P.E.P. §2131.

Claim 1 as amended is directed to a method of identifying a candidate p21 pathway modulating agent using an assay system comprising mammalian cultured cells that express a CSNK1G polypeptide or nucleic acid, contacting the assay system with a candidate test agent that modulates the expression of CSNK1G, determining the level of cell proliferation in the assay system in the presence and absence of the test agent, and selecting the test agent as a candidate p21 pathway modulating agent if the level of cell proliferation in the assay system contacted with the test agent is altered relative to the level of cell proliferation in the assay system not contacted with the test agent.

The Office argued that Funk et al. anticipates claim 1 because it allegedly teaches that bone marrow derived dendritic cells from TNF-receptor knock-out mice survive in culture and proliferate in response to CSF and that TNF-receptor deficient cells have reduced levels of p21 protein. The Office concluded that Funk et al. teach a method of identifying a modulator of the p21 pathway, TNF, by measuring cell proliferation and a second assay measuring p21 protein levels. The Office surmised that the dendritic cells are likely to express CSNK1G, based on the teachings of Kusuda et al.. which allegedly teaches that CSNK1G expression is ubiquitous.

However, the claims recite a method of identifying a candidate p21 pathway modulating agent using an assay system comprising cells that express a CSNK1G polypeptide or nucleic acid and contacting the assay system with a candidate test agent that modulates the expression of CSNK1G. First, Funk et al. was studying the effects of TNF and CSF on the growth of dendritic cells and thus its teachings are not in any way directed to developing screening assays for identifying various p21 pathway modulating agents. Further, given that Funk et al fails to even mention CSNK1G, it fails to contemplate any association between CSNK1G and p21, and certainly fails to contemplate identifying a p21 pathway modulating agent using a test agent that modulates the expression of CSNK1G.

Thus, Funk et al. fails to anticipate the claimed invention because it fails to teach each and every element as set forth in claim 1 and fails to describe the identical invention in as complete

detail as is contained in the claim. Accordingly, Applicants respectfully request withdrawal of the 35 USC 102(b) rejections in view of Funk et al.

35 USC § 103 Rejections

Claims 1, 2, 6, and 16 were rejected under 35 USC 103(a) as being allegedly obvious over Donato et al. (J. Biol Chem, 273: 5067-5072 (1998)) in view of Funk et al., as evidenced by Kusuda et al. Claims 2 and 6 have been cancelled, rendering the rejection moot with respect to those claims. Applicants respectfully traverse the rejection with respect to the pending claims.

The Office alleged that Donato et al teach a process for identifying TNF and the protease inhibitor YVAD as modulators of the p21 pathway. The Office admitted that Donato et al do not teach a method for identifying modulators of the p21 pathway, wherein the process includes a cell proliferation assay. However, the Office argued that Funk et al. teaches a cell proliferation assay and that it would have been obvious to a person of ordinary skill in the art to combine the teachings of Donato et al and Funk et al to develop a process for identifying TNF and YVAD as modulators of the p21 pathway, wherein the process includes a cell proliferation assay. The Office further asserted that the ME-180 cells of Donato et al are likely to express a CSNK1G, as evidenced by Kusuda et al. The Office further stated that the expectation of success is high, as cell proliferation assays are well-known in the art.

Applicants respectfully submit that, like Funk et al., the Donato et al. reference fails to even mention CSNK1G, fails to contemplate any association between CSNK1G and p21, and thus fails to contemplate identifying a p21 pathway modulating agent using a test agent that modulates the expression of CSNK1G. In the absence of any teaching whatsoever in Donato et al, Funk et al, and Kasuda et al. of a connection between CSNK1G and the p21 pathway, much less a method for identifying a p21 pathway modulating agent by contacting cells that express a CSNK1G polypeptide or nucleic acid with a test agent that modulates the expression of CSNK1G, the cited references do not, alone or in combination, teach the presently claimed methods.

For the reasons set forth above, the cited references do not render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of the 35 USC 103(a) rejections over Donato et al. in view of Funk et al., as evidenced by Kusada et al.

CONCLUSION

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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